



RESEARCH ARTICLE

COMPARATIVE STUDY ON THROMBOEMBOLIC EVENTS AMONG SUBJECTS WITH TYPE 2 DIABETES MELLITUS AT KING ABDULAZIZ MEDICAL CITY IN SAUDI ARABIA

Naif M. Alhawiti<sup>1</sup>, Ibrahim W. Alanzan R. S<sup>1</sup>, Abdulrahman A. Alharbi<sup>1</sup>, Mohieldin Elsayid<sup>1</sup>, Dr. Raniah S. Alotibi<sup>1</sup>, Maaged A. Akiel<sup>1</sup>, Dr. Hassan S. Alamari<sup>1</sup> and Dr. Shoeb Qureshi<sup>2</sup>

<sup>1</sup>Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh.

<sup>2</sup>Research Methodology Unit, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh

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ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) is characterized by insensitivity to insulin, which is linked with many pathological alterations leading to cardiovascular diseases. Consequently, enormous studies indicated that patients with T2DM are significantly associated with blood vascular diseases, in particular thromboembolic complications.

**Aim of study:** This study was designed to study the prevalence of thromboembolic complications among Saudi patients diagnosed with T2DM and identify the most common types of thromboembolic complications in patients with T2DM.

**Methodology:** Retrospective cohort study was performed on medical records of 150 Saudi patients diagnosed with T2DM at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia between January 2015 and January 2017. Review included demographic data, biochemical, hematology, coagulation profiles and thromboembolic complications.

**Results:** A total of 150 patient records with T2DM were interrogated in this retrospective study. All patients showed significantly increased fasting glucose and HbA1c levels. Around 18 diabetic patients (7.33% males and 4.66% females) developed thrombotic events between January 2015 and 2017. Hematological results demonstrated that most subjects were diagnosed with anemia based on levels of hemoglobin and red blood cell count. Reduction in platelet counts were observed among T2DM patients suffering from thrombosis compared to control subjects, which suggests increased consumption of platelets in patients with thrombotic complications. Consequently, coagulation profiles showed hypercoagulability state in T2DM patients with thrombosis in comparison to controls. We also observed deep vein thrombosis in 38.9% of T2DM patients with thrombotic events. This observation infers that deep vein thrombosis is the most common type of thromboembolic events among T2DM patients.

**Conclusion:** The prevalence of thromboembolic complications is greater among Saudi patients who are diagnosed with T2DM in which represents a major clinical health problem and a healthcare burden. Although the high incidence and serious nature of thrombosis, a national prevention program should be developed to understand the risk factors of thromboembolic events within T2DM patients and to find out a proper management and treatments.

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INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is one of the most clinical and public health problems in the world, which is characterized by insensitivity to insulin. T2DM is a multifactorial disorder with considerable genetic heterogeneity (Zimmet, 2001).

Consequence of impaired response to insulin (Ogurtsova, 2017; Elhadd, 2007 and Lipscombe, 2007). Hyperglycaemia is frequently related with cardiovascular complications, particularly in promotion of atherosclerosis as well as vascular thrombosis (Chait, 2009). Globally in 2015, it is estimated that approximately 415 million individuals diagnosed with T2DM aged between 20-79 years, and almost 5.0 million people died

due to diabetic complications (Alqurashi, 2011). The international diabetes Federation (IDF) estimated that the number of individuals with T2DM will increase to 439 million in 2030 and 642 million in 2040 (Al-Nozha, 2004 and Kumar, 2011). In Saudi Arabia, the overall prevalence of T2DM was reported to be 34.1% in males and 27.6% in females. Due to consequences of life-style (as of fat-diet, lack of exercise, increase number obesity, and smoking), T2DM is more predominant in Saudi community particularly in major cities such as Riyadh and Jeddah (Alqurashi, 2011 and Al-Nozha, 2004). Sequence of reference 6 and 8 T2DM is highly associated with a the proinflammatory and prothrombotic state (Kumar, 2011 and Navarro, 2006). The entire functions of platelet and coagulation is impaired in patients with diabetes. Consequently, circulated activated platelets in T2DM patients adhere to vascular endothelium, unlike in healthy individuals, additional platelets aggregate within vessels. Raised levels of plasma coagulation factors and inhibited fibrinolytic pathways potentiate both thrombosis and defective formed clot lysis (Ruggeri, 1997, Ruggeri, 2002; Vinik, 2001 and Creager, 2003). Thus, the majority of cardiovascular diseases related to T2DM complications intricate by blood vessel occlusion are initially triggered via pathophysiology of endothelial cell dysfunction, platelet activation and coagulation reactivity (Davi, 2007; Deanfield, 2007; Fuentes, 2012; Fuentes, 2011 and Jackson, 2007). The risk of atherosclerosis, arterial thrombosis, pulmonary embolism and deep venous thrombosis as vascular diseases were significantly potentiated by concomitant cardiovascular risk factor, such as diabetes mellitus (Jackson, 2015). The national healthy survey reported that increased the incidence of T2DM among Saudi population is alarming for the healthcare because a serious complications such as vascular diseases, which are associated with T2DM, lead to morbidity and mortality (Al-Nozha, 2004). So, T2DM is considered a major threat for Saudi community in both genders. Although, the challenge is to identify the patients with T2DM at risk of developing thrombosis still encountered the physicians. However, identifying the prevalence of T2DM and the quantity of diabetic patients with high risk of thrombotic development is necessary for future preventive plans. The present study aimed to report the update in prevalence of thromboembolic events, hematological and coagulation profile changes that occurred in T2DM patients.

## PATIENTS AND METHODS

This is a retrospective study of T2DM Saudi patients was conducted at King Abdulaziz Medical City, Riyadh, Saudi Arabia from January 2015 to January 2017. The medical records of 150 patients were observed for demographic characteristics, medical history and laboratory data (hematological, biochemical and coagulation profiles). The sample size was obtained through calculation using the online sample size calculator (Check Market) providing a marginal error of 5% at 95% confidence level. The cohort subjects participated in this study were randomly selected and included. Both genders who are 18 years old and older. In this study, T2DM individuals diagnosed with or without thrombosis after January 2015 until January 2017 were included, however, T2DM patients diagnosed with thrombotic events prior to January 2015 and/or diagnosed with other diseases such as leukemia, tumor lesions, liver disease, kidney disease were excluded. This study was approved by the Institutional Review Board (IRB), (IRB approval # IRBC/859/17) at King Abdullah International Medical Research Center (KAIMRC). Data were

collected from the electrical medical record system in the King Abdulaziz Medical City and entered into Microsoft Excel file and then submitted for analysis using Statistical Package for GraphPad Prism software program version 6 (GraphPad, San Diego, CA, USA). Data were expressed as mean  $\pm$  standard deviation (SD) or as percentage distribution. Statistical analysis was determined using one-way analysis of variance (ANOVA).  $P$ -value  $\leq 0.05$  was considered statistically significant.

## RESULTS

**Baseline characteristics of patients:** Data of 150 patients (79 males and 71 females) diagnosed with T2DM were analyzed. Table 1 summarize the characteristics of diabetic patients without thromboembolic ( $n = 132$ ) and with thromboembolic events ( $n = 18$ ). All T2DM patients participated in this study had significantly greater fasting glucose levels and HbA1c concentrations compared to non-diabetic subjects (controls), ( $P < 0.001$  and  $P < 0.008$  respectively). Thrombotic complications frequently occurred in older diabetic patients more than younger patients. Results displayed significant differences compared to control subjects ( $P < 0.045$ ). Analysis of body weight and body mass index (BMI) of T2DM patients without or with thrombosis showed no significant difference compared to healthy controls.

**Lipid and liver profile in T2DM patients with and without thrombotic events:** Total cholesterol and triglycerides in T2DM patients without or with thrombosis were slightly increased when compared with control subjects. We did not observe significant change between T2DM patients and controls (Table 2) and in lipid profile between T2DM patients with thrombotic complications compared to patients without thrombotic complications. In addition, no significant difference was reported in the levels of aspartate aminotransferase (AST), and alanine aminotransferase (ALT) between T2DM patients with or without thrombosis and control subjects. Nevertheless, significantly lowered plasma levels of albumin was observed in both T2DM patients with or without thrombosis compared with healthy controls ( $P < 0.001$ ).

**Hematological profiles in T2DM patients with and without thrombotic events:** As shown in Table 3, both T2DM patients without or with thrombosis showed significantly decreased levels of hemoglobin and hematocrit with alteration in the red blood cell count (RBC), when compared with healthy subjects, but mean cell volume (MCV) and mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) were within normal range. In addition, the results exhibited no alteration in the white blood cell count (WBC). The data analysis showed that T2DM without or with thrombotic events is associated with decreased platelet count compared to healthy population, but no significant differences were observed. Overall, the hematological data also showed that most T2DM patients either with or without thrombotic complications suffered from anemic lesion.

**Coagulation parameters in T2DM patients with and without thrombotic events:** T2DM either without with thrombotic complication exhibited a shorter international normalized ratio (INR) and Activated Partial Thromboplastin Time (APTT) compared to controls, with no statistical significance ( $P > 0.05$ , Table 4). The results also may indicate a hypercoagulable state, which potentially affects both extrinsic and intrinsic coagulation pathways.

**Table 1. Baseline characteristics of controls and T2DM patients with and without thrombotic events**

Demographics	Control (Mean±SD), N=30	Without thrombosis (Mean±SD), n=132	With Thrombosis (Mean±SD), n=18	P Value
Gender (M/F)	16/14	68/64	11/7	---
Age (Year)	27.63±7.91	58.8±12.111	66.63±10.296	0.045
Weight (kg)	89.03±10.19	75.16±13.253	73.51±18.321	0.548
BMI(kg/m <sup>2</sup> )	30.97±2.94	29.80±5.53	28.61±7.27	0.280
Fasting Glucose(mmol/L)	4.88±1.25	15.74±2.89	16.01±2.96	0.001
HbA1c(%)	5.23±0.52	7.71±1.25	8.06±1.50	0.008

Abbreviations: M, male; F, female; BMI (body mass index), HbA1c (hemoglobinA1C blood test); T2DM (type 2 diabetes mellitus). Data are represented as Mean±SD, and the *P* value ≤ 0.05 is considered statistically significant.

**Table 1. Lipid profile and liver profile in type 2 diabetic mellitus patients with and without thrombotic events**

Parameter		Control (Mean±SD), n=30	With Thrombosis (Mean±SD), n=132	With Thrombosis (Mean±SD), n=18	P value
Lipid Profile	HDL (mmol/L)	1.28±0.25	1.01±0.38	0.97±0.33	0.102
	LDL (mmol/L)	2.03±0.56	2.91±0.62	3.01±0.96	0.095
	Total Cholesterol (mmol/L)	3.59±0.95	4.18±1.30	5.00±1.41	0.059
	Triglycerides (mmol/L)	0.92±0.50	1.22±1.06	1.64±1.48	0.351
Liver Function Profile	AST(U/L)	18.01±9.91	22.02±5.98	24.11±8.43	0.081
	ALT (U/L)	36.30±12.89	33.98±5.92	34.65±6.50	0.853
	Albumin (g/L)	40.98±7.31	29.08±7.41	25.36±8.09	0.001

Abbreviations: HDL, (high-density lipoproteins); LDL, (low-density lipoproteins); AST, (aspartate aminotransferase); ALT, (alanine aminotransferase). Data are represented as Mean ± SD, and the *P* value ≤ 0.05 is considered statistically significant.

**Table 2. Peripheral blood hematological parameters for T2DM patients with and without thrombotic events**

Parameter	Control (Mean±SD), n=30	Without Thrombosis (Mean±SD), n=132	With Thrombosis (Mean±SD), n=18	P Value
WBC Count (x10 <sup>9</sup> /L)	6.40±1.68	7.20±2.32	6.50±2.11	0.648
RBC Count (x10 <sup>12</sup> /L)	4.71±0.91	3.56±0.95	3.61±0.73	0.028
Hemoglobin(g/dL)	0.44±0.07	0.31±0.09	0.33±0.10	0.018
MCV(fL)	87.00±6.12	83.61±16.62	81.50±14.00	0.651
MCHC	338.87±14.65	310.10±45.06	312.15±36.27	0.147
RDW (%)	13.50±1.25	17.30±3.49	18.13±4.02	0.021
Platelet Count (x10 <sup>9</sup> /L)	286.87±75.91	239.12±152.07	188.87±109.33	0.212
MPV(fL)	8.84±0.42	9.07±0.32	9.04±0.47	0.686

Abbreviations: WBC (white blood cell), RBC (red blood cell), MCV (mean cell volume), MCH (mean cell hemoglobin), MCHC (mean cell hemoglobin concentration), RDW (red distribution width). Data are represented as Mean ± SD, and the *P* value ≤ 0.05 is considered statistically significant.

**Table 4. Platelet indices and coagulation parameters in T2DM patients with and without thrombotic events**

Parameter	Control (Mean±SD), n=30	Without Thrombosis (Mean±SD), n=132	With Thrombosis (Mean±SD), n=18	P Value
INR	1.04±0.27	2.47±1.22	1.76±0.27	0.074
APTT (Secs)	38.06±2.87	36.63±3.88	33.30±2.61	0.124

Abbreviations: INR (international normalized ratio), APTT (activated partial thromboplastin time). Data are represented as Mean ± SD, and the *P* value ≤ 0.05 is considered statistically significant.

### Prevalence of thrombotic events among T2DM patients:

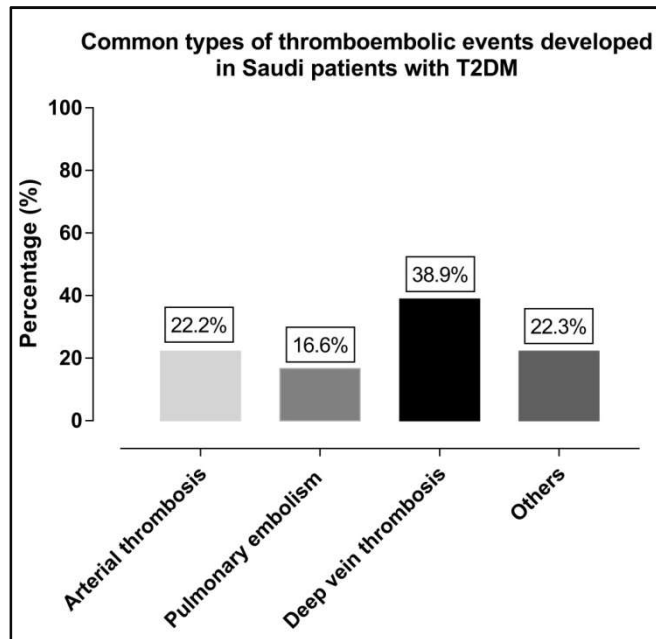
Figure 1 shows the distribution of development of different types of thromboembolic events among Saudi patients diagnosed with T2DM. Deep vein thrombosis (DVT) was found to be highly more prevalent in diabetic patients with 38.9%, while arterial thrombosis was frequently developed in 22.2%; pulmonary embolism was the lowest prevalence of 16.6%. Other types of thromboembolic events such as atherosclerosis, peripheral arterial disease and stroke were highly prevalent (22.3%) within patients with T2DM. Moreover, comparing the prevalence of thromboembolic events with respect to the gender of patients showed that male subjects with T2DM have higher prevalence than female subjects by 7.33% and 4.66% respectively as shown in Figure 2.

Overall, the data of the present study indicate that T2DM patients have a high risk of thromboembolic progression, and male patients may encounter higher incidence for vascular thrombosis complications than female at older age.

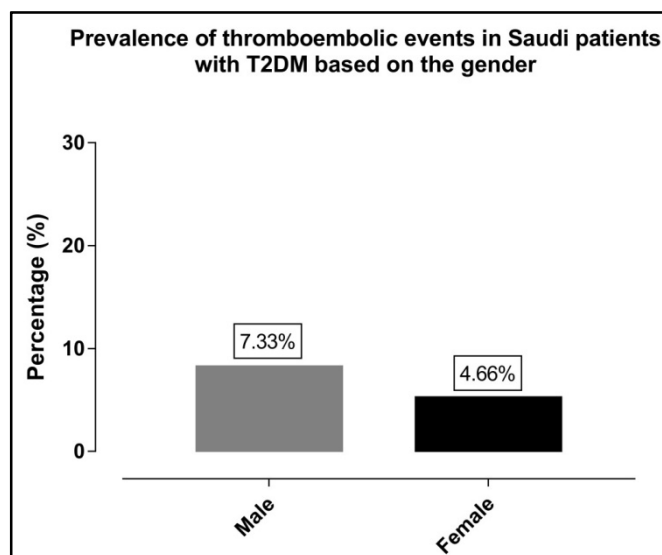
## DISCUSSION

It is well-established that T2DM has a significant involvement in the alteration of cardiovascular and hemostatic system (Heather, 2011; Grundy, 1999). Patients with T2DM have high risk for the development of cardiovascular diseases such as arterial thrombosis; atherosclerosis and deep venous thrombosis (DVT) through triggering of different mechanisms

including hypercoagulation, platelet hyperactivity and endothelium dysfunction (Vinik, 2001; Kakouros, 2011; Laakso, 1998 and Undas, 2008). Thus, cardiovascular diseases are responsible for a greater number of morbidity and mortality among T2DM patients in the worldwide especially in Western countries (Kumar, 2011 and Creager, 2003). In Saudi Arabia, national epidemiological healthy survey was carried out within Saudi community; the analyzed data showed that 4004 subjects out of 16917 (23.7%) were diagnosed with T2DM. the diabetes prevalence was observed in urban community than rural (Al-Nozha, 2004 and Naeem, 2015).



**Figure 1. Common types of thrombotic events developed among Saudi populations diagnosed with T2DM (data represented as %)**



**Figure 2. Prevalence of thrombotic complications in different gender of Saudi populations diagnosed with T2DM (data represented as %)**

The current study was proposed to evaluate the frequency of thrombotic complications among Saudi patients diagnosed with T2DM. This study included approximately 150 Saudi patients at King Abdulaziz Medical City, 79 males and 71

females diagnosed with T2DM during the period of January 2015 to January 2017. Our data displayed that prevalence of thrombotic complications among T2DM patients is higher in males at older ages than female, which was consistent with the previous findings. Published observational and clinical data demonstrated that T2DM concomitantly occurs with aging and are associated with increased risk of cardiovascular diseases in particular, pathologic thrombus formation (Alqurashi, 2011; Wild, 2004 and Guariguata, 2014). In this retrospective study, the analyzed data showed that LDL, total cholesterol and triglycerides levels were slightly increased in the diabetic patients with thrombosis, while HDL was faintly decreased when compared with non-diabetic healthy subjects, and the results did not reach statistical significance (Table 2). As reported in the literature reviews, an elevation in levels of LDL, total cholesterol and/or triglycerides highly plays a key role in the mechanisms of atherogenesis to potentiate thromboembolic formation particularly within those diabetic patients (Ogbera, 2009 and Monteiro, 2016). Interestingly, our study revealed that serum albumin levels significantly diminished in T2DM patients diagnosed with thrombosis compared to control subjects (Table 2). Djoussé *et al* stated that the reduction of serum albumin concentrations in the presence of concomitant cardiovascular risk factor such as diabetes mellitus greatly potentiates increased risk of arterial and/or venous thrombosis (Djoussé, 2006). Moreover, previous studies demonstrated that a lower level of serum albumin is linked with 2-fold augmented risk of cardiovascular disease (Weijenberg, 1997 and Gillum, 1992). The authors, thus highlighted that determination of albumin levels in the serum of diabetic patients could help in identifying individuals at risk of thrombosis (Djoussé, 2002 and Gillum, 1992). T2DM is known as chronic disease, often accompanied by mild to moderate anemia, which recognized as anemia of chronic disease (de Carvalho, 2006 and Andrews, 2012). As consistent with this thought, the most common hematological manifestations shown in this study were diminished values of hemoglobin, red blood cells and hematocrit in T2DM patients with or without thrombotic events compared with non-diabetic healthy subjects, which can be related to normocytic normochromic anemia (Table 3). Shortening the survival of red blood cells is most common characteristics observed in anemia of chronic disease (de Carvalho, 2006). These findings showed that diabetic patients with anemia expose insufficient bone marrow activity observed is due mostly to inappropriate erythropoietin production, and diminished erythropoiesis resulting in lower secretion of iron to the bone marrow. Thus, the most cause that participates to anemia progression within diabetic patients is nutritional deficiencies. Although those patients have low iron contents but showing that ferritin increases in their serum which associated with chronic inflammatory disorders in diabetic patients (Wrede, 2006; Thomas, 2005 and Symeonidis, 2006). Furthermore, potentiated expression of proinflammatory molecules and cytokine production is significantly increased in diabetic patients with anemia than diabetic patients without anemia (35). In addition, the prevalence of proinflammatory cytokines in diabetic patients that were anemic promotes the risk of cardiovascular complications such as arterial thrombosis, stroke and atherosclerosis (Zhang, 2014). Platelets are well-known to have a key role in both physiological and pathological hemostasis (Fuentes, 2012; Furie, 2008; George, 2000). It is suggested that the defective platelet count and/or platelet dysfunction have a crucial involvement in enhancement of thrombotic activity that would be associated with an

increased incidences in patients at high risk for cardiovascular disease such as T2DM (Davi, 2007; Gawaz, 2005; Gibbins, 2004 and Andrews, 2004). In this study, decreased platelet counts were observed in T2DM patients with thrombosis compared to T2DM without thrombosis ( $188.87 \pm 109.33$  versus  $239.12 \pm 152.07$ ), although did not reach statistical significance. This indicates that the presence of thrombotic complications may associated with lower platelet count. Possible explanation for this lower platelet count in T2DM patients with thrombosis is the elevated consumption of circulated platelets in blood stream in the existence of vascular adverse. Moreover, the evaluation of coagulation profiles included INR (extrinsic coagulation pathway) and APTT (intrinsic coagulation pathway), the most hemostatic parameters routinely performed in hematology laboratory for assessing hemostatic activity. Our data showed a shorter INR and APTT in T2DM patients with thrombotic complications as compared to control subjects, but no statistical significance was detected. Indeed, hypercoagulability is frequently reported in patients who under risk of blood vascular complications. Hypercoagulability refers to an imbalance of anti-versus pro-coagulation system that would lead to potentiate a thrombogenic phenotype and thrombus formation. In addition to procoagulable state, defective fibrinolysis is one of important mechanisms involving micro- and macrovascular thrombi development in diabetic patients (Tripodi, 2009; Tripodi, 2011 and Mann, 2011). Overall, increased platelet activation and coagulation reactivity within patient's blood circulation is crucial risk factor for thromboembolic formation and vascular inflammation though involving in intricate mechanisms (Vinik, 2001; Furie, 2008; Gawaz, 2005; Tripodi, 2011).

The national healthy survey reported that increased incidence of T2DM among Saudi population is alarming for the healthcare because serious complications such as vascular diseases associated with T2DM frequently lead to morbidity and mortality (Al-Nozha, 2004). In our study, the prevalence of thromboembolic events was 7.33% of male and 4.66% of female subjects with T2DM compared to patients with T2DM without thrombosis (Figure 1). Previous study demonstrated that diabetes prevalence is slightly higher in males than females at older ages (Wild, 2004). As explored in literature, diabetic patients have high risk for vascular disease by 2-5 folds than non-diabetic individuals (Guariguata, 2014). As reported that the prevalence of diabetic mellitus among males more than female, therefore males as expected will be at high risk to cardiovascular disorders than females (Al-Nozha, 2004 and Mohieldein, 2014). As shown in Figure 1, the present study reported that the incidence of DVT was 38.9%, arterial thrombosis was 22.2% and pulmonary embolism was 16.6% among patients with T2DM. However, 22.3% of other thromboembolic types such as stroke, atherosclerosis and peripheral occlusive vascular disease were recorded in different diabetic patients (Figure 2). Petrauskiene *et al* suggested that diabetes has high impact on the development of DVT than arterial thrombosis through its influence on coagulation pathways, in particular fibrinolysis more severely than platelets, and that could probably have a greater influence on the progression of DVT versus other kinds of thrombosis (Petrauskiene, 2005). Furthermore, the authors concluded that diabetic mellitus may be an independent risk factor for cardiovascular complications in patients. An impaired component of hemostasis system in diabetic mellitus has been stated in enormous research studies. An alteration of hemostatic system in T2DM is significantly leading to prompt

risk of pathologic thrombosis (Chait, 2009; Grundy, 1999 and Tripodi, 2011). The existence of activated platelets, fibrin, and coagulation hyperactivity in peripheral blood circulation through secretion of various thrombogenic adhesive molecules such as collagen, von Willebrand factor (VWF), and tissue factor is a crucial mechanism for thromboembolic disease development. Furthermore, in response to platelet activation, other cells such as leukocytes and endothelial cells are recruited and activated in vivo to contribute to thromboembolic mechanism via release of the pro-inflammatory molecules such as cytokines and chemokines leading to trigger the secondary thrombus formation (18, 19, 52). In conclusion, the overall prevalence of thromboembolic complications within patients with T2DM in Saudi Arabian is alarming, reaching 7.33% in males and 4.66% in females in our cohort. Late diagnosis of diabetic patients who are at high risk of thrombotic complications will ultimately result in vascular adverse complications with increasing burden of disease. More importance should be carried out on the job of healthcare clinics in the screening, management, treatment and providing public awareness of cardiovascular disease development. Great prospective multicenter studies are advised to promote the change of lifestyle of diabetic patient that will be a vital helpful manner in the prevention of thromboembolic complications since T2DM can be managed by following healthy lifestyle.

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